REGULUS THERAPEUTICS

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microRNA Therapeutics: Targeting the Pathways of Human Disease

Regulus Therapeutics is a biopharmaceutical company created to discover, develop and commercialize microRNA (miRNA) therapeutics. Formed as a joint venture between Isis – a pioneer in oligonucleotide drug technologies and a leader in the field of antisense therapeutics, and Alnylam – a leader in the field of RNAi therapeutics, Regulus intends to address therapeutic opportunities that arise from abnormal expression or mutations in microRNAs. Since microRNAs regulate networks of genes and biological pathways, microRNA therapeutics define a new strategy to target multiple points on disease pathways. Regulus has assembled a top executive team with corporate management, business and scientific expertise to lead the new venture. Regulus' advisory board consists of world-class scientists and the foremost authorities in the field of microRNA research. In addition, Regulus has been formed combining the leading capabilities and intellectual property estates of its two parent companies. Regulus' intellectual property portfolio consists of more than 900 patents and patent applications, of which over 600 are issued. Thus, in Regulus, its founders have created the leading microRNA therapeutics company, a company that will translate one of the most important new frontiers in modern biology into an entirely new approach for innovative medicines by targeting the pathways of human disease with microRNA therapeutics. Regulus maintains facilities in Carlsbad, California.

Therapeutic Programs

Regulus is developing a comprehensive R&D portfolio that is built on microRNA biology, chemistry and informatics to support several therapeutic programs in oncology, immunology-inflammation and metabolics. In addition, Regulus is focusing on two target-specific drug discovery programs, one with emphasis on miR-122 and another on a currently undisclosed microRNA target.
Regulus' most advanced program is a microRNA therapeutic that targets miR-122 for the treatment of hepatitis C virus (HCV) infection, a significant disease worldwide where emerging therapies target viral genes and are therefore prone to viral resistance. We are targeting miR-122, an endogenous host microRNA required for viral infection by HCV.

About microRNAs

microRNAs represent a new approach for the treatment of human disease. Most RNAs, such as messenger RNAs, are transcribed from genes and are used to make proteins through the process of translation. Recently, an entirely new category of RNAs was discovered: microRNAs or miRNAs. Like messenger RNAs, miRNAs are also transcribed from genes. However, these small miRNAs do not encode proteins but have been found to regulate the expression of other genes. There are more than 700 microRNAs that have been identified in the human genome, and these are believed to regulate the expression of one-third of all human genes by preventing translation of messenger RNAs into proteins. miRNAs thus act as master regulators for physiological pathways or genetic networks to achieve integrated biological functions. This ability to affect the expression of multiple genes in the pathway of disease makes miRNAs an exciting new platform for drug discovery and development. When inappropriately expressed or mutated, miRNAs represent disease targets whose selective antagonism can result in broad modulation of points on a disease pathway in a manner that is not easily achievable by today's medicines. The in vivo work on miRNAs pioneered by Alnylam and Isis has demonstrated effective down-regulation of miRNAs and consequent effects on therapeutically relevant processes. To date, miRNAs have been implicated in several disease areas, such as cancer, viral infection, and metabolic disorders.

Partnerships and Collaborations

GlaxoSmithKline (GSK)

In April 2008, GSK and Regulus Therapeutics announced the first ever microRNA-focused strategic alliance to discover, develop and market novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The alliance provides GSK with an option to license drug candidates directed at four different microRNA targets with relevance in inflammatory disease. Regulus will be responsible for the discovery and development of the microRNA antagonists through completion of clinical proof of concept. Once optioned, GSK will have an exclusive license to each drug developed by Regulus for the relevant microRNA target for further development and commercialization on a worldwide basis.

Collaborations

A key aspect of Regulus' R&D strategy is to collaborate with leading academic labs in order to expand the identification and understanding of microRNA biology. Currently Regulus has many microRNAs under evaluation through collaborative research programs. This extensive network, with the world's top laboratories, positions Regulus at the leading edge of the field of microRNA to then capitalize and translate those discoveries into developmental and clinical programs.

Intellectual Property

The combination of Isis and Alnylam IP estates for microRNA therapeutics creates what we believe is an unparalleled patent position for pharmaceutical products that target microRNAs.
Regulus has been granted exclusive licenses to both Isis' and Alnylam's intellectual property for microRNA applications. This includes a portfolio of over 900 patents and patent applications, of which over 600 are issued, owned by Isis pertaining to chemical modification of oligonucleotides for therapeutic applications. In addition, Regulus has acquired rights to a large estate of patents and patent applications accumulated by both Alnylam and Isis in the field of microRNA therapeutics, including early fundamental patents in the field of microRNAs, such as the Tuschl III, Tuschl IV and Esau patents.

Publications

Isis and Alnylam scientists and collaborators were the first to discover microRNA antagonist strategies that work in vitro and in vivo in animal studies. These publications include:

* Esau *et al.* (2004) *J Biol Chem*., 279, 52361-52365
* Krutzfeldt *et al.* (2005) *Nature*, 438, 685-689
* Esau *et al.* (2006) *Cell Metab*., 3, 87-98
* Davis *et al.* (2006) *Nucleic Acids Res*., 34, 2294-304
* Krutzfeldt *et al.* (2007) *Nucleic Acids Res*., 35, 2885-92
* Li *et al.* (2007) *Cell*, 129,147-61
* Esau, Monia. (2007) *Adv Drug Deliv. Rev*., 59, 101-14
* Dolken *et al.* (2007) *J Virol*., 24, 13771-13782
* Gottwein *et al.* (2007) *Nature*, 450, 1096-1099
* Gabriely *et al.* (2008) *Mol. Cell. Biol.*, 28(17), 5369-80

Board of Directors

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